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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/987,931	11/16/2001	Kevin Qun Fang	4821-439-999	7960

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EXAMINER	
KIM, VICKIE Y	

ART UNIT	PAPER NUMBER
1618	

DATE MAILED: 08/08/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/987,931	FANG ET AL.	
	Examiner	Art Unit	
	Vickie Kim	1618	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 127-132 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 127-132 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

RCE acknowledged

A request for continued examination(RCE) under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 6/16/06 has been entered.

Status of Application

1. Acknowledgement is made of amendment filed 6/16/06. Upon entering the amendment, the claims 1-126 are canceled and claims 127-132 are amended.

2. The pending claims are 127-132 and presented for the examination.

Response to Arguments

Applicant's arguments filed 6/16/06 with respect to claims have been considered but are moot in view of the new ground(s) of rejection due to the scope changes made into the newly amended claims.

Claim Rejections - 35 USC § 112, 1st

1. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Scope of Enablement

Claims 127-132 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims because the specification, while being enabling for TREATING an affective disorder(e.g. anxiety disorder) in a patient in need thereof, does not reasonably provide enablement for preventing said affective disorders as claimed using a compound as claimed.

Attention is directed to In re Wands, 8 USPQ 1400 (CAFC 1988) at 1404 (CAFC 1988) at 1404 where the court set forth the eight factors to consider when assessing if a disclosure would have required undue experimentation. Citing Ex parte Forman, 230 USPQ 546 (BdApls) at 547 the court recited eight factors:

1) *The nature of the invention:*

The instant invention is drawn to a treatment of an affective disorder using an effective amount of bupropion metabolite(i.e. (2S, 3S)-2-(3-chlorophenyl)-3,5,5-trimethyl-2-morpholinol as claimed in claim 127.

2) *The state of the prior art:*

As the state of art recognizes, there are numerous path-etiologic factors(e.g.bio-pathways and pathogens) involved in developing such neurological disorders as claimed and not fully understood yet. As evidenced by numerous documents, an affective disorders(e.g. anxiety

disorder, depression, etc) is not known as preventable disorders but treatable. The state of the art recognizes that the significance of particular drug treatment for modifying different aspects of biological activity cannot be predicted a priori and furthermore, the treatment of bupropion metabolite may not be significantly altering or influencing all the possible path-etiologic factors, and furthermore, it is impossible to avoid all the possible factors triggering these bio-pathways. The state of the art also recognizes that a drug treatment can not be effectively preventing the claimed diseases where complexed etiologic factors are involved in different level and strength. And thus, a single drug therapy is selectively effective and used in the treatment of the specific condition(s) but not for preventing the claimed diseases, see supporting document enclosed in PTO-892, e.g. Disease-Major depression (dr greene.com, see second page);Anxiety disorders(CNN.com./Health, see second page); .

3) *The relative skill of those in the art:*

The relative skill of the those in the art is high.

4) *The predictability of the art:*

The high degree of **unpredictability** in pharmacological activity in general and the drug treatment is well known in the art, especially in the field of treating neurological disorders. A slight change in the structure of the drug would drastically change its influence on receptor binding activity and selectivity. Note that in cases involving physiological activity such as

the instant case, " the scope of enablement obviously varies inversely with the degree of unpredictability of the factors involved". See In re Fisher, 427 F 2d 833, 839, 166 USPQ 18, 24 (CCPA 1970).

For a pharmaceutical composition containing multiple active ingredients or carriers having different chemical structures and modes of actions, their interaction, co-action, e.g. synergism etc. is even more unpredictable. The specification does not provide any competent evidence or disclosed tests that are highly predictive for the pharmaceutical use of the instant compounds in the treatment of all the claimed conditions.

5) *The breadth of the claims and The amount of guidance/working examples::*

Applicant's assertion that the inventive compounds and its composition would be useful for preventing anxiety completely does not commensurate with the scope of the objective enablement, especially in view of the high degree of unpredictability without working examples. It is noted that however, the claims must be given their broadest reasonable interpretation. Therefore, the interpretation of claims (i.e. prevention of affective diseases) should be made based on the full definition of the term "prevention" including "forestall affective disease completely" wherein the claims become not enabled.

An extensive research investigation is made into various diseases and conditions as claimed caused by numerous patho-etiologic factors

(not fully understood) in the human body as it interplays with nutrition, genetics, Stress and impaired immunity and the complex factors which are normally responsible for the outbreaks of such conditions and diseases. Furthermore, the present invention deals with various conditions and diseases which are not classified together nor have same manifestations.

With lack of evidentiary support, it is beyond the skill of skilled artisan today to get an agent to prevent all the claimed conditions(e.g. anxiety) completely.

The specification provides lack of evidential support substantially where any skilled artisan can not clearly understand how the claimed invention(i.e. a method of treating diseases as claimed) is made and used at the time of the invention with the information provided and thus, the claims are considered not enabled with the information given.

7) *Quantitation of undue experimentation.*

Since insufficient teaching and guidance have been provided in the specification, one of ordinary skill in the art, even with high degree of skill, would not be able to use the composition as claimed without undue experimentation except for treating affective disorders in need thereof using the invention composition containing bupropion metabolite.

The true fact of the state of the art is expressed well, "The significance of particular drug treatment for modifying different aspects of biological activity cannot be predicted a priori but must be determined from the case to case by painstaking

experimental study and when the above factors are weighed together, one of ordinary skill in the art would be burdened with undue "painstaking experimentation study " to determine the efficacy against all the diseases as claimed.

To obviate this rejection, applicant is advised to amend the claims in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims. It is noted that the specification is only enabling for TREATING or reducing the occurrence of affective disorder(e.g. anxiety disorder) in a patient.

Claim Rejections - 35 USC § 103

3. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

4. Claims 127-132 are rejected under 35 U.S.C. 103(a) as being unpatentable over Morgan (US6274579, 6391875, 2003/0064988) in view of Spier (1998, abstract only, Use of bupropion with SRIs and venlafaxine).

Note: all these patents are children cases of US6274579 and disclosures therein are substantially same. Therefore, the examiner will use US'579 to represent all these cases.

The claims are drawn to a method of treating or preventing an affective disorders such as obesity(weight gain), or coccain addiction, attention deficit hyperactivity disorder(ADHD) by administering a therapeutically or prophylactically effective amount

of a bupropion metabolite such as (+)-(2S, 3S)-2-(3-chlorophenyl)-3,5,5-trimethyl-2-morpholinol and adjunctively effective amount of secondary active compound.

Morgan et al(US'579) teaches a compound (+)-(2S, 3S)-2-(3-chlorophenyl)-3,5,5-trimethyl-2-morpholinol and its composition used for treating depression, attention deficit hyperactivity disorder(ADHD), obesity or addiction to cocaine or nicotine containing product(e.g. tobacco), see abstract.

The critical elements required by the claims are well taught by the cited reference(s) except that they required secondary active compound such as SSRI or 5HT compound..

However, it would have been obvious to one of ordinary skill in the art at that time of the invention was made to add secondary active agent when Morgan(US'579) is taken in view of Spier's reference because latter reference teaches the combination drug treatment wherein bupropion is main active agent combined with an effective amount of secondary active agent effectively used in the treatment of various affective disorders.

Spier teaches a combination drug of bupropion and SRI's in the treatment of depression, see abstract. It also teaches that the drug response is superior in combination drug therapy compared to monotherapy.

Since Morgan teaches that bupropion's anti-depressant activity is resulted from the active metabolite in vivo, i.e. (+)-(2S, 3S)-2-(3-chlorophenyl)-3,5,5-trimethyl-2-morpholinol(see col. 8, lines 15-20), one would have been motivated, with reasonable expectation of success, to add SSRI or 5HT compound as secondary active compound

into antidepressant(i.e. (+)-(2S, 3S)-2-(3-chlorophenyl)-3,5,5-trimethyl-2-morpholinol) to treat affective disorders because the combination drug treatment improves efficacy by lowering side effects and achieve additive pharmacological effect because these agents are utilizing different underlying mechanisms as taught in Cary and Howard references. It is clearly suggested in later references that combination drug treatment could enhance drug efficacy and improve industrial applicability as well. Furthermore, combination drug therapy is standard drug regimen well known in the field of psychiatry medicine, see extrinsic supporting documents PTO-892, for instance, Zarate(2003, Combination treatment in bipolar disorder) or Post et al(1997,previously cited).

One would have been motivated to combine these references and make the modification because they are drawn to same technical fields (constituted with same ingredients and share common utilities, and pertinent to the problem which applicant concerns about. MPEP 2141.01(a).

5. Claims 127-132 are rejected under 35 U.S.C. 103(a) as being unpatentable over Howard et al(US6677678) or Cary (WO99/17803) in view of Morgan et al((US6274579).

The claims are drawn to a method of treating or preventing an affective disorders such as obesity(weight gain), or coccain addiction, attention deficit hyperactivity disorder(ADHD) by administering a therapeutically or prophylactically effective amount of a bupropion metabolite such as (+)-(2S, 3S)-2-(3-chlorophenyl)-3,5,5-trimethyl-2-morpholinol and adjunctively effective amount of secondary active compound.

Firstly, Howard et al (US'678 hereinafter) teach SSRI(serotonin selective reuptake inhibitors) used in the treatment of affective disorders such as major depressive disorder. Furthermore, in the background section, US'736 teaches an advantages obtained from a combination drug treatment of SSRI and bupropion(see col. 1, lines 10-25) where synergism and reduction of side effects can be seen in combination of SSRIs and bupropion drug treatment.

Secondly, Cary(WO'803) also teaches a nicotine or other substance addiction treatment such as cocaine or alcohol addiction by applying a combination drug regimen where bupropion and nicotine receptor antagonists such as fluoxetine(SSRI), imipramine(5HT), mecamylamine are effectively used as active agent, col.4, lines 5-38.

The claims are differ in that they require bupropion's metabolite rather than bupropion itself.

As mentioned earlier,(supra), Morgan teaches that bupropion's anti-depressant activity is resulted from the active metabolite in vivo, i.e. (+)-(2S, 3S)-2-(3-chlorophenyl)-3,5,5-trimethyl-2-morpholinol(see col. 8, lines 15-20).

In light of Morgan(US6274579) teaching, one would have been motivated, with reasonable expectation of success, to substitute bupropion with its active metabolite (i.e. (+)-(2S, 3S)-2-(3-chlorophenyl)-3,5,5-trimethyl-2-morpholinol), and administer combination drug(i.e. SSRI or 5HT compound as secondary active compound into antidepressant(i.e. bupropion metabolite) to treat affective disorders because the metabolite is the active form where optimal drug dosage regimen can be used for determining most efficient drug treatment. Additionally combination drug treatment can

be benefited by optimal dose used in the treatment because it could maximally lower side effects and furthermore, achieve additive or synergistic pharmacological effect because these agents are utilizing different underlying mechanisms as taught in Cary and Howard references.

All the critical elements required by the instant claims are well taught in the cited reference and thus, the claimed subject matter is not patentably distinct over the prior art of the record.

Double Patenting

6. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

7. Claims 127-132 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 13-15 and 58 – 78 of copending Application No. 09/987930 in view of Spier, Howard or Cary(see above in 103 rejection). both inventions are drawn to the similar invention where the scoped of the invention is overlapping substantially. For the same reason set forth in 103 rejection, the claimed subject matter shared overlapping scope(i.e. a treatment of

affective disorders using (2S, 3S)-2-(3-chlorophenyl)-3,5,5-trimethyl-2-morpholinol) and the combination with secondary is clearly envisioned when secondary teaching is taken together.

This is a provisional obviousness-type double patenting rejection.

Conclusion

1. No claim is allowed.

2. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Vickie Kim whose telephone number is 571-272-0579. The examiner can normally be reached on Tuesday-Friday.
If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Hartley be reached on 571-272-0616. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

VICKIE KIM
PRIMARY EXAMINER

Vickie Kim
August 3, 2006
Art unit 1618